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Thalidomide attenuates multiple low-dose streptozotocin-induced diabetes in mice by inhibition of proinflammatory cytokines

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ABSTRACT

Thalidomide is an immunomodulatory and anti-inflammatory agent and is used in autoimmune disorders. It has been shown that thalidomide inhibits proinflammatory cytokines production. The purpose of this study was to investigate the effect of thalidomide on the prevention of autoimmune diabetes in mice. Diabetes was induced by multiple low-dose of streptozotocin (MLDS) injection. Mice were treated with thalidomide (300 mg/kg/day orally) for 21 days. Plasma levels of glucose, insulin and nitrate/nitrite as well as pancreatic cytokine levels were measured. Pathological examinations of the pancreas revealed that thalidomide reduced the islet inflammation (insulitis) and destruction of beta cells. Thalidomide treatment prevented hyperglycemia and preserved pancreatic insulin secretion in the diabetic mice. Thalidomide treatment also significantly decreased plasma levels of nitric oxide and pancreatic proinflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-12, IL-17 and interferon (IFN)-γ)] while increased anti-inflammatory cytokine IL-10. In conclusion, these findings indicate that thalidomide may have a protective effect against the autoimmune destruction of the pancreatic beta-cells during the development of MLDS-induced type 1 diabetes in mice.

1. Introduction

Type 1 diabetes is a T-cell mediated autoimmune disease characterized by the selective destruction of insulin-producing β-cells in the pancreatic islets of Langerhans. Chronic pancreatic inflammation (insulitis) and destruction of islet β-cells in type 1 diabetes is mediated by the immune cells, particularly autoreactive CD4 and CD8 T lymphocytes, B-cells, macrophages and dendritic cells [1]. T-cells can directly destroy β-cells through a cytotoxic process, and they can also destroy β-cells through the secretion of proinflammatory cytokines. Moreover, in response to cytokine stimulation, β-cells generate reactive oxygen species (ROSs) and reactive nitrogen species such as nitric oxide (NO), which facilitate their destruction [2]. NO is also synthesized within cytokine-activated macrophages by inducible nitric oxide synthase (iNOS) [3]. T helper 1 cells produce proinflammatory cytokines (TNF-α, IFN-γ, IL-1β, IL-6, IL-12) which activate macrophages and cytotoxic T cells to destroy β-cells, whereas IL-4 and IL-10 cytokines that are produced by activated T helper 2 cells, prevent β-cell destructive insulitis [4].

Experimental insulin-dependent diabetes can be induced by multiple low doses of streptozotocin (STZ) (MLDS) in rodents [5]. MLDS is a commonly used animal model that has many histological and clinical features similar to those of human type 1 diabetes and involves the participation of macrophages and T cells. STZ is a pancreatic β-cell toxin that induces inflammation of the islets by immune cells when it is given in multiple low doses [6]. The MLDS model has been used widely to study the immunological pathways that lead to β-cell death and progressive hyperglycemia.

It has been shown that some drugs such as thalidomide have immunomodulatory and anti-inflammatory activity, which might represent a potential preventive therapy for autoimmune diseases. Thalidomide (α-N-phthalimido glutarimide) is a glutamic acid derivative that was first introduced in 1954 as a sedative drug but was withdrawn from the market due to its teratogenic effects. Thalidomide has various pharmacological properties and it has been used successfully for various inflammatory and autoimmune diseases. Thalidomide was approved by the FDA for the treatment of erythema nodosum leprosum (ENL) and multiple myeloma [7]. It has also been demonstrated that thalidomide or its analogs are effective in the treatment of rheumatoid arthritis, Crohn's disease, prostate cancer, Behcet's disease, chronic host-versus-graft disease, lupus erythematosis and HIV-associated oral ulcers [8–11]. However, teratogenicity, peripheral neuropathy and other adverse effects of thalidomide have led to the design of its new analogs.

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